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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,549	06/07/2001	John SantaLucia JR.	WSU 0192 PUSP	7537

7590 12/16/2003

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EXAMINER

KENEDY, ANDREW A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,549	SANTALUCIA ET AL.	
	Examiner	Art Unit	
	Andrew A. Kenedy	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-60 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Priority

With regard to claims 1-60, applicants are accorded benefit to provisional application No. US 60209778, having a filing date of June 7, 2000.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-60 are rejected under 35 U.S.C. 102(a) due to disclosure of the invention by the applicants to the public more than one year before the priority date of the instant application.

Applicants disclosed the HYTHER™ program at the 217th National Meeting of the American Chemical Society (ACS) on March 24, 1999, as documented by applicants' IDS document Peyret et al. ("A new program for the prediction of DNA hybridization thermodynamics." American Chemical Society, March 1999, abstract number BIOT-121) and examiner's search result for ACS website past meetings listing (see attached webpage copy, and references cited). Specifically, the method, system, and computer-readable storage medium comprising the HYTHER™ computer program were disclosed by the applicants at the ACS National Meeting in the form of a written abstract and poster communications.

The provisional application (US 60209778), to which priority is claimed, discloses the HYTHERTM computer program as possessing all of the limitations of claims 1-60 (refer to section 1 of the provisional application, paragraphs entitled "Background" and "Thermodynamic Parameters" (no page numbering by applicants); and sections 2 and 3 of the provisional application (pages numbered 2-17)). As HYTHERTM was disclosed at the ACS National Meeting, it appears that all of the features of the applicants' invention as claimed in the instant nonprovisional application were also disclosed at the ACS National Meeting on March 24, 1999.

Claims 1-12, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Barciszewski & Clark (RNA Biochemistry and Biotechnology, 1999, pg. 11-43).

Barciszewski & Clark teach a method for predicting nucleic acid hybridization thermodynamics, the method comprising: providing a database of thermodynamics parameters (see at least page 1, paragraphs 1-3 of the Abstract); receiving hybridization information which represents at least one sequence (see at least pg. 25, lines 29-31); receiving correction data (see at least pg. 26, lines 1-8); receiving a first set of data which represents hybridization conditions (see at least pg. 11, lines 28-32); and calculating hybridization thermodynamics including net hybridization thermodynamics based on the hybridization information, the thermodynamic parameters, the correction data and the first set of data (see at least pg. 11, lines 32-34; and pg. 22, lines 12-14); wherein the hybridization thermodynamics of individual single stranded, bimolecular and higher order complexes are statistically weighted in a numerical process and the equilibrium concentration of each species is output (see at least pg. 31, line 18 through pg. 33, line 5; pg. 41, lines 14-17); wherein the correction data includes folding

correction data (see at least pg. 26, lines 9-23); wherein the correction data includes linear correction data (see at least pg. 26, lines 3-5); wherein the thermodynamic parameters include DNA thermodynamic parameters (see at least pg. 11, line 27; pg. 26, lines 1-2; and pg. 23, lines 7-10); wherein the DNA thermodynamic parameters include dangling end parameters (see at least Fig. 7; and pg. 21, lines 29-35); wherein the DNA thermodynamic parameters include coaxial stacking parameters (see at least pg. 35, lines 1-4; and pg. 23, lines 7-9); wherein the DNA thermodynamic parameters include terminal mismatch parameters (see at least pg. 15, lines 25-30; and pg. 23, lines 7-9); wherein the thermodynamic parameters include RNA thermodynamic parameters (see at least pg. 11, lines 24-27); wherein the thermodynamic parameters include hybrid DNA/RNA thermodynamic parameters (see at least pg. 11, lines 27-28; and pg. 23, lines 9-10); wherein the thermodynamic parameters include DNA loop thermodynamic parameters (see at least Fig. 5; and pg. 15-21); wherein the hybridization information represents top and bottom strand sequences which form a duplex and wherein the hybridization thermodynamics are calculated for the duplex (see at least pg. 1, lines 27-28; and pg. 23, lines 9-10); and calculating the concentration of each species in a solution at a plurality of temperatures (see at least pg. 31, line 18 through pg. 33, line 5; pg. 41, lines 14-17; pg. 35, lines 23-32).

Since the methods disclosed by Barciszewski & Clark are implemented using computer systems (see at least the abstract on pg. 1-2), the system of claims 21-32, and 38, and the computer-readable storage medium of claims 41-52, and 58, are anticipated for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barciszewski & Clark in view of Lane et al. (US 6027884 A).

Barciszewski & Clark are applied as above.

Barciszewski & Clark teach receiving hybridization information for nucleic acid sequences. This hybridization information could be for nucleic acid sequences that are targets and primers/probes; however, they do not specifically mention this possibility.

Lane et al. teaches a method of thermodynamic analysis of nucleic acid hybridization wherein the hybridization information represents at least a section of a target and a length of at least one primer or probe complimentary to the target; wherein the hybridization thermodynamics are calculated for a plurality of primers or probes complimentary to the target; wherein the hybridization information represents at least a section of a target and a primer or probe; wherein a length of the target is longer than a length of the primer or probe and wherein the hybridization thermodynamics are calculated for a best target/primer or target/probe complex and for competitive mismatch complexes; wherein hybridization information represents at least a section of a target and a primer or probe and wherein a length of a target is longer than the length of the primer or probe and wherein the hybridization thermodynamics are calculated for a

best target/primer or target/probe complex and for competitive target/primer or target/probe complexes (see at least col. 1, lines 32-60; col. 4, lines 4-9; col. 20, line 28 through col. 21, line 36; col. 23, lines 21-49).

It would have been obvious for one of ordinary skill in the art to incorporate the receiving of hybridization information representing at least a section of a target and a length of at least one primer or probe complimentary to the target, the receiving of hybridization information representing at least a section of a target and a primer or probe, and the calculating of hybridization thermodynamics for a plurality of primers or probes complimentary to the target, into the method of Barciszewski & Clark, since Lane et al. teaches that "detecting the presence or absence of a target sequence or sequences, which if present in a subject, indicates that the subject is suffering from or predisposed to an infection (e.g., septicemia) by an organism or virus related to the target sequence or sequences, e.g., a protozoan, viral, bacterial, or yeast sequence." (col. 21, lines 49-55); that "primers of the invention can be used to test a single sample of a biological fluid, e.g., blood, serum, plasma, or urine, for the presence of multiple target sequences in a single reaction, e.g., to detect the presence of a plurality of disease causing organisms in a single reaction. In particular, the primers are useful for detecting organisms which contribute to septicemia, e.g., a bacterium, e.g., a gram negative bacterium, an anaerobic infectious agent, a streptococcal agent, a staphylococcal agent, a pneumococcal agent, E. coli, or pseudomonas." (col. 5, lines 39-49); and that "detecting the presence or absence of a target sequence or sequences, which if present in a subject, indicates that the subject is suffering from or predisposed to a disorder, e.g., an inherited disorder, related to the target sequence or sequences." (col. 21, lines 56-61).

Since the methods disclosed by Barciszewski & Clark are implemented using computer systems (see at least the abstract on pg. 1-2), the system of claims 33-37, and the computer-readable storage medium of claims 53-57 are obvious for the same reasons.

Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barciszewski & Clark and Lane et al.

Barciszewski & Clark and Lane et al. are applied as above. As discussed previously, while Barciszewski & Clark do not specifically teach that the hybridization information could be information for nucleic acid sequences that are targets and primers/probes, Lane et al. does teach this aspect. Like Barciszewski & Clark, Lane et al. teaches the prediction of nucleic acid hybridization thermodynamics in a solution at a plurality of temperatures (col. 33, line 63 through col. 34, line 4).

Lane et al. does not teach calculating the concentration of every species in a solution.

As discussed previously, Barciszewski & Clark teach calculating the concentration of every species in a solution.

Upon combining the teachings and methods of Barciszewski & Clark and Lane et al. based on the motivations provided previously regarding claims 13-17, the resulting combined method would provide a method wherein the hybridization information also represents a primer or probe and wherein the length of the target is longer than a length of the primer or probe and wherein the hybridization thermodynamics are calculated for a best target/primer or target/probe complex and for competitive mismatch complexes and wherein the method further comprises

calculating the concentration of every species in a solution at a plurality of temperatures; and wherein the hybridization thermodynamics are calculated for at least two best target/primer or target/probe complexes and for their corresponding competitive mismatch complexes and wherein the method further comprises correcting for any interactions between the at least two best target/primer or target/probe complexes and their components.

This would have been obvious to one of ordinary skill in the art based on the content of the individual teachings and methods of Barciszewski & Clark and Lane et al., and the motivation to combine as discussed above.

Since the methods disclosed by Barciszewski & Clark are implemented using computer systems (see at least the abstract on pg. 1-2), the system of claims 39-40, and the computer-readable storage medium of claims 59-60 are obvious for the same reasons.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Applicants' listed IDS documents which disclose various aspects of applicants' instant invention, but do not anticipate the invention as claimed, include Allawi et al. (*Biochemistry*, 1997); Allawi et al. (*Biochemistry*, 1998); Allawi et al. (*Biochemistry*, Vol. 37, No. 8, 1998); Allawi et al. (*Nucleic Acids Research*, 1998); Antao et al. (*Nucleic Acids Research*, 1992); Blake et al. (*Bioinformatics*, 1999); Blommers et al. (*Biochemistry*, 1989); Bommarito et al. (*Nucleic Acids Research*, 2000); Breslauer et al. (*PNAS*, 1986); Chen et al. (*Biotechniques*, 1997); Fotin et al. (*Nucleic Acids Research*, 1998); Freier et al. (*PNAS*, 1986); Gray (*Biopolymers*, Vol. 42, 1997, pg. 795-810); Gray (*Biopolymers*, Vol. 42, 1997, pg. 783-793);


Haas et al. (*Nucleic Acids Research*, 1998); Hillier et al. (*PCR Methods and Applications*, 1991); Hyndman et al. (*Biotechniques*, 1996); Kadrmas et al. (*Nucleic Acids Research*, 1995); Ke et al. (*Biochemistry*, 1995); Kierzek et al. (*Biochemistry*, 1999); Ladbury et al. (*Biochemistry*, 1994); Leontis et al. (*Nucleic Acids Research*, 1991); Liuni et al. (*Biotechniques*, 1998); Mathews et al. (*Journal of Molecular Biology*, 1999); Mathews et al. (*RNA*, 1999); Mitsunashi et al. (US 5556749); Owczarzy et al. (*Biopolymers*, 1998); Peyret et al. (*Biochemistry*, 1999); Proutski et al. (*Cabios Applications Note*, 1996); Rychlik et al. (*Nucleic Acids Research*, 1989); SantaLucia, Jr. (*PNAS*, 1998); SantaLucia, Jr., et al. (1998); SantaLucia, Jr. et al. (*Biochemistry*, 1996); SantaLucia, Jr., et al. (*Biopolymers*, 1998); Xia et al. (*Biochemistry*, 1998); Zucker (*Science*, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew A. Kenedy whose telephone number is 703-305-4842 (after January 12, 2003, use telephone number 571-272-0574). The examiner can normally be reached on Monday-Friday 9:00am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-305-4842.

AAK
December 11, 2003


MARIANNE P. ALLEN
PRIMARY EXAMINER
AU1631